Ketamine and serotonin syndrome: A case report

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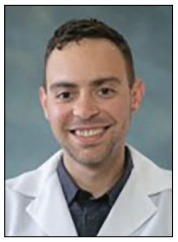
Long utilized as a rapid anesthetic, ketamine has been increasingly used in sub-anesthetic doses for several psychiatric indications, including depression, suicidality, and chronic pain. Recently, an intranasal form of esketamine—the S-enantiomer of ketamine—was FDA-approved for treatment-resistant depression. Previously, researchers believed ketamine mediated its analgesic and psychotropic effects solely via *N*-methyl-D-aspartate (NMDA) receptor antagonism, but emerging research has described a seemingly more complex receptor profile.[1] One such ancillary pharmacologic mechanism is occupation of the serotonin receptor.[1,2] However, there is sparse literature describing the possible extent of ketamine's involvement in serotonin syndrome.[3] Here, we describe a case of serotonin syndrome that might have been induced by ketamine.

CASE REPORT

Ms. O, age 41, has a history of endometriosis, anticardiolipin antibody syndrome, major depressive disorder, and generalized anxiety disorder. She initially presented to an outside hospital and was admitted for chronic endometriosis pain. During that admission, her pain was treated with IV ketamine, 40 mg/hour, on hospital Days 1 through 4. While hospitalized, she continued to receive her home medications: fluoxetine, 40 mg/d, coumadin, 5 mg/d, and diphenhydramine, 25 mg/d. On Day 5, Ms. O experienced visual hallucinations and was diagnosed with ketamine-induced delirium. She was treated with haloperidol (dose unknown) with reportedly good effect. On Day 7, she was discharged home.

Upon returning home, she experienced persistent altered mental status. Her significant other brought her to our hospital for further workup. Ms. O's body temperature was 37.6°C, and she was diaphoretic. Her blood pressure was 154/100 mm Hg, and her heart rate was 125 bpm. On physical examination, she had 4+ patellar and Achilles reflexes with left ankle clonus and crossed adductors. Her mental status exam showed increased latency of thought and speech, with bizarre affect as evidenced by illogical mannerisms and appearance. She said she was "not feeling myself" and would stare at walls for prolonged periods of time, appearing internally preoccupied and confused.

Ms. O was treated with IV lorazepam, 2 mg. Fourteen hours later, her temperature returned to normal, but she remained tachycardic, hypertensive, and altered. She received 2 additional doses of 2 mg and 1 mg. Seventeen hours after the initial dose of IV lorazepam was administered (and 3 hours after the second dose), Ms. O's heart rate returned to normal. She was ultimately converted to oral lorazepam, 1 mg every 12 hours. Two hours later, Ms. O's blood pressure



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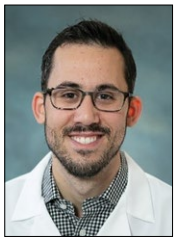

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returned to normal, and her physical exam showed normal reflexes.

Ms. O was given a presumptive diagnosis of ketamine-induced serotonin syndrome. She made a good recovery and was discharged home.

A suspected association

Serotonin syndrome is caused by increased levels of the neurotransmitter serotonin in the CNS. Clinical features of serotonin syndrome include agitation, restlessness, mydriasis, altered mental status or confusion, tachycardia, hypertension, muscle rigidity, diaphoresis, diarrhea, piloerection, headache, fasciculations, clonus, and shivering. Severe cases can be life-threatening and may present with high fever, seizures, arrhythmias, and loss of consciousness. Serotonin syndrome is a clinical diagnosis; the Hunter Serotonin Toxicity Criteria are often used to make the diagnosis. To meet these criteria, a patient must have received a serotonergic agent, and at least one of the following must be present[4]:

- spontaneous clonus
- inducible clonus and agitation or diaphoresis
- ocular clonus and agitation or diaphoresis
- tremor and hyperreflexia
- hypertonia, temperature >38°C, and ocular clonus or inducible clonus.

For Ms. O, we suspected that administration of ketamine in conjunction with fluoxetine, 40 mg/d, led to serotonin syndrome. Ms. O exhibited ocular clonus and diaphoresis, thus satisfying the Hunter Serotonin Toxicity Criteria, and she also had inducible clonus, altered mental status, hypertension, and tachycardia, which makes serotonin syndrome the most likely diagnosis. She improved after receiving lorazepam, which is often used to treat hypertonicity, decrease autonomic instability, and prevent seizures seen in serotonin syndrome.[5]

There is sparse literature describing serotonin syndrome related to ketamine use. Ketamine has been shown to increase levels of glutamate in the medial prefrontal cortex. Higher levels of glutamine in turn stimulate excitatory glutamatergic neurons that project to the dorsal raphe nucleus. When stimulated, the dorsal raphe nucleus releases serotonin.[6] There is also evidence that ketamine inhibits uptake of serotonin in synapses.[7] These mechanisms combine to create a net increase in CNS-wide serotonin.

Ketamine is being increasingly used to treat depression and other conditions. This case report underscores the importance of considering serotonin syndrome when treating patients receiving ketamine, especially when it is used in conjunction with selective serotonin reuptake inhibitors.

Clinical Point

We suspected that administration of ketamine in conjunction with fluoxetine, 40 mg/d, led to serotonin syndrome

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